with minor effect in *2/*2 carriers. After 900mg LD, the effect of the CYP2C19*2 variant on platelet inhibition was fully compensated in wt/*2 carriers but not in *2/*2 carriers (–83.6±25.8% in wt/wt vs. –77.2±26.9% in wt/*2 vs. –29.5±26.8% in *2/*2; overall p-value=0.0003, p=0.20 for wt/wt versus wt/*2, p<0.001 for wt/*2 versus *2/*2). A similar pattern was observed for the active metabolite AUC0-6 and there was a significant correlation between PK and PD responses irrespective of the LD.

Conclusion: Carriers of CYP2C19*2 display significant lower responses to clopidogrel with a gene dose-effect. Clopidogrel resistance can be overcome by increasing the dose in heterozygous carriers but not in homozygous carriers.

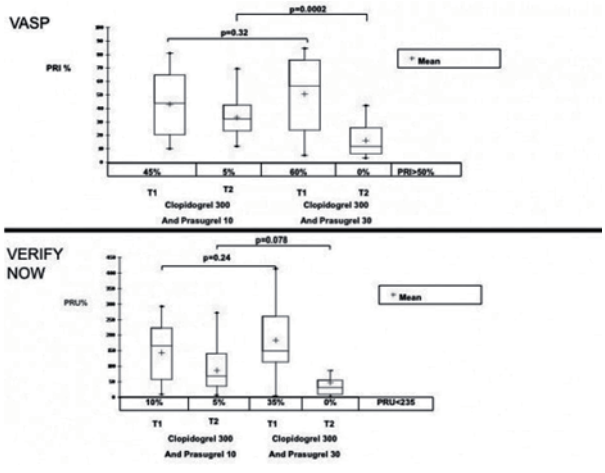
035

Switching patients from clopidogrel to prasugrel at the early phase of an acute coronary syndrome: impact of prasugrel reloading

Simon Méjean [Orateur] (1), Thibault Lhermusier (2), C Garcia (3), Vincent Bataille (1), Caroline Biendel (1), Nicolas Boudou (1), Nicolas Dumonteil (1), Michel Galinier (1), Pierre Sié (1), Didier Carrié (1)
(1) CHU Rangueil, Maladies Cardiovasculaires et Métaboliques, Toulouse, France – (2) CHU Rangueil, Maladies Cardiovasculaires et Métaboliques, Toulouse, France – (3) CHU Rangueil, Laboratoire d'Hémostase, Toulouse, France

Purpose: There is no consensus on how to manage the switch from clopidogrel to prasugrel immediately after a clopidogrel loading dose (LD). The aim of this study was to evaluate the pharmacodynamic response of switching patients in this situation and comparing two prasugrel reloading doses (RD) by using three laboratory tests. Methods: Patients hospitalized for acute coronary syndrome (ACS) who received a 300 mg LD of clopidogrel before admission were referred for inclusion. Their platelet response to the P2Y12 inhibitor was tested with vasodilator-stimulated phosphoprotein phosphorylation (VASP), Verify Now assay and light transmission aggregometry (LTA) on admission (T1). Then, patients were immediately randomized for 2 RD of prasugrel (10 mg or 30 mg) and platelet response was tested again by the same methods (T2). Results: 20 patients were included in each group. All T1 and T2 analyses were performed during the first 24 hours after hospitalization. Compared with a 300 mg LD of clopidogrel, the proportion of patients with platelet hyporesponsiveness for VASP to the P2Y12 inhibitor was lower after the prasugrel RD: 8 vs 1 (p<0.001) in the 10 mg prasugrel group and 12 vs none (p<0.001) in the 30 mg prasugrel group. Late adenosine diphosphate-induced platelet aggregation (LPA), by LTA was lower after a 30 mg prasugrel RD compared with a 10 mg RD (mean LPA 8 +/–9 vs 14 +/–12; p<0.001). Similar results were found using VerifyNow P2Y12 (mean PRU 38 +/–60 vs 87 +/–71; p < 0.001) and VASP assays (mean PRI 17 +/– 12 vs 33 +/–15; p<0.001). No bleeding events were reported during the hospital stay.

Conclusions: For patients receiving 300 mg clopidogrel therapy after an ACS, a 30 mg RD of prasugrel compared to a 10 mg RD is associated with further reduction in platelet function and markedly decreases the proportion of P2Y12 inhibitors low responders.



Platelet inhibition tested by Verify Now and VASP

036

Long-term dual antiplatelet treatment and clinical outcome of diabetic patients treated with drug-eluting stents

Vassilis Voudris [Orateur] , Panagiotis Karyofyllis, Constantinos Doulaptsis, Ioannis Moukas, Sophia Thomopoulou, Dennis Cokkinos
Onassis Cardiac Surgery Center, Cardiology Dpt, Athens, Greece

Background: Despite encouraging short and mid-term results with drug-eluting stents (DES) in diabetic (DM) patients (pts) with coronary artery disease, the long-term efficacy is controversial. We assessed the influence of long-term dual antiplatelet treatment (DAPLT) with aspirin and clopidogrel on clinical outcome of DM pts treated with DES.

Methods: The study included 610 consecutive DM pts (male 80%, mean age 65±9 years) that had been treated with DES. Five years clinical follow-up (FU) obtained in 584/610 (96%) of them. At the end of follow-up, 341 (58%) pts were on DAPLT and 243 (42%) on single antiplatelet treatment (SAPLT). The primary end-point was the combination of death (D), non-fatal myocardial infarction (MI) and cerebrovascular accident (CVA), and was considered as hard end-point (HEP). Stent thrombosis (ST) occurring -12 months after DES implantation was considered as early (EST), and for >12 months, as late (LST). The ARC definition for ST was used.

Results: There was no difference in gender, age, risk factors profile, unstable coronary artery disease, insulin treatment, extent of coronary artery disease, and systolic left ventricular function between the two groups. At 12 months post PCI 546 (92%) pts were on DAPLT; the incidence of EST (definite or probable) was 0.8%. The incidence of LST (definite or probable) was 0.7%. There was no difference in the incidence of ST in pts treated with DAPLT vs. SAPLT (1.4% vs. 1.6%, p: ns). At FU, HEP was observed in 18% vs. 13%, in pts on DAPLT vs. SAPLT (p: ns).

Conclusion: Long-term DAPLT in DM pts treated with DES implantation is not associated with better clinical outcome or lower risk of definite or probable ST.

037

Incidence and predictors of coronary stent thrombosis: evidence from an international collaborative meta-analysis including 32 studies, 222,752 patients, and 4490 thromboses

Gilles Lemesle [Orateur] (1), Fabrizio D'Ascenzo (2), Mario Bollati (2), Bo Lagerqvist (3), Ron Waksman (4), Jose De La Torre Hernandez (5), Gregg Stone (6), Antonio Colombo (7), Piergiovanni Buonamici (8), Giuseppe Biondi-Zoccai (9)
(1) CHRU Cardiologie, Centre Hémodynamique, Lille, France – (2) University of Turin, Division of Cardiology, Turin, Italia – (3) Uppsala Clinical Research Centre, Uppsala University, Division of Cardiology, Uppsala, Sweden – (4) Washington Hospital Center, Washington DC, United-States – (5) Hospital Marques de Valdecilla, Division of Cardiology, Santander, Spain – (6) Columbia University Medical Center and the Cardiovascular Research Foundation, New-York, Ny, United-States – (7) Centro Cuore Columbus, Milan, Italia – (8) Careggi Hospital, Department of Cardiology, Florence, Italia – (9) University of Modena and Reggio Emilia, Division of Cardiology, Modena, Italia

Background: Stent thrombosis remains among the most feared complications of percutaneous coronary intervention (PCI) with stenting. However, data on its incidence and predictors are sparse and conflicting.

Objective: We aimed to perform a collaborative systematic review on incidence and predictors of stent thrombosis. PubMed was systematically searched for eligible studies from the drug-eluting stent (DES) era (1/2002-12/2010).

Methods: Studies were selected if including ≥2,000 patients undergoing stenting or reporting on ≥25 thromboses. Study features, patient characteristics, incidence and predictors of stent thrombosis were abstracted and pooled, when appropriate, with random-effect methods (point estimate [95% confidence intervals]).

Results: A total of 32 studies were identified (222,752 patients, 4,490 thromboses), with DES used in 89%. After a median of 22 months, definite, probable, or possible stent thrombosis had occurred in 2.3% (2.0%; 2.6%), with acute in 0.3% (0.2%; 0.5%), subacute in 1.1% (0.9%; 1.3%), late in 0.5% (0.4%; 0.6%), and very late in 0.6% (0.4%; 0.7%). Similar figures were computed for studies reporting only on DES, except for lower rates of acute ST (0.2% [0.1%; 0.2%]). From a total of 47 candidate variables, the most reliable predictors of definite/probable stent

▶

thrombosis were acute coronary syndrome at admission, diabetes, and stent number/length. Age, extent of coronary disease, renal failure and smoking also appeared as significant predictors, but less consistently. Premature discontinuation of dual antiplatelet therapy was also a powerful predictor of stent thrombosis.

Conclusions: Despite numerous possible risk factors, the strongest predictors of stent thrombosis are diabetes, acute coronary syndromes, stent length/number, and premature discontinuation of dual antiplatelet therapy.

038

Uninterrupted oral anticoagulation in association with short term dual antiplatelet therapy: the most reasonable antithrombotic strategy for warfarin patients?

Pierre-François Lesault [Orateur] (1), Stéphane Champagne (1), Thibaud Damy (2), Gauthier Mouillet (1), Patrick Dupouy (3), Thierry Joseph (4), Hakim Benamer (5), Abdel Belarbi (1), Dionyssis Pongas (2), Barnabas Gellen (2), Jean-Luc Dubois-Randé (2), Emmanuel Teiger (1)
(1) AP-HP, CHU Henri Mondor, Laboratoire d'Hémodynamique et de Cardiologie Interventionnelle, Créteil, France – (2) AP-HP, CHU Henri Mondor, Fédération de Cardiologie, Créteil, France – (3) Clinique des Fontaines, Melun, France – (4) AP-HP, CHU Ambroise-Paré, Boulogne, France – (5) Clinique la Roseraie, Aubervilliers, France

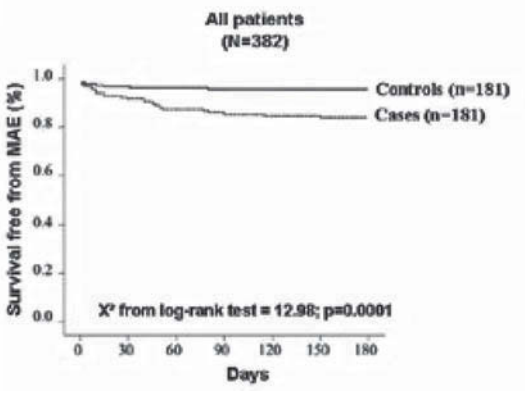
Objectives: To assess the impact on 6-month post-stenting outcomes of long-term vitamin K antagonist (VKA) therapy at baseline and of continued versus discontinued VKA therapy.

Background: Dual antiplatelet therapy (DAT) after stenting is associated with higher bleeding event rates in patients on long-term VKA therapy at stenting.

Methods: Matched case-control study in patients who underwent stenting at four centers between July 2003 and October 2006. Matching was on age, sex, and clinical presentation.

Results: We included 181 patients on VKA therapy at stenting and 181 controls. VKA therapy was continued after stenting in 60% of the cases. The 6-month major adverse event rate (primary endpoint defined as the association of death, myocardial infarction, stent thrombosis, major bleeding or stroke) was significantly higher in the cases than in the controls (odds ratio [OR], 3.3; 95% confidence interval [95%CI], 1.5-6.9; ***P***<0.01). The cases had higher rates of death (OR, 3.8; 95%CI, 1.0-14.0; ***P***=0.05) and major bleeding (OR, 5.4; 95%CI, 1.5-18.9; ***P***<0.01). DAT duration was significantly shorter in the cases left on VKA therapy but did not differ according to stent type. By multivariable analysis, significant predictors of the MAE rate in the cases were GpIIb3a treatment during stenting (hazard ratio [HR], 7.4; 95%CI, 1.8-29.7; ***P***<0.01) and age (HR per year 1.05; 95%CI, 1.0-1.1; ***P***=0.03). There was a non significant reduction in MAE and major bleeding for cases at 6 months if VKA therapy were continued in association with DAT after stenting (rate of MAE: 8.3 vs. 15.7% for discontinued VKA therapy, p=0.26, rate of major bleeding 3.8 vs 9.7 p=0.16).

Conclusions: Long-term VKA therapy at stenting is associated with increased bleeding events and poor outcomes. Continued VKA therapy with close INR monitoring and a short DAT duration may be appropriate in patients on long-term VKA therapy at stenting.



Kaplan Meier Curves for MAE

039

Benefit of tailored therapy with high clopidogrel maintenance dose according to CYP2C19 genotypes in clopidogrel non responders undergoing coronary stenting for acute coronary syndrome

Thomas Cuisset [Orateur] (1), Jacques Quilici (1), Pierre E Morange (2), Jean Louis Bonnet (3), Marie Christine Alessi (2)
(1) AP-HM, CHU La Timone, Cardiologie Interventionnelle, Marseille, France – (2) AP-HM, CHU LA Timone, Inserm, U626, Laboratoire d'Hématologie, Marseille, France – (3) AP-HM, CHU La Timone, Cardiologie, Marseille, France

Objectives and background: Loss-of-Function allele CYP2C19*2 has been associated with impaired clopidogrel response and worse prognosis in clopidogrel-treated patients. Benefit of Tailored therapy according to platelet function test remains unclear and potential effect of genotypes on this benefit has not been addressed in unstable patients. The present study was designed to evaluate the benefit of tailored therapy with higher maintenance dose according to CYP2C19 genotypes in patients identified as non responders undergoing Percutaneous Coronary Intervention (PCI) for Non ST segment Elevation Acute Coronary Syndrome (NSTE ACS).

Methods and results: 346 consecutive patients were enrolled, who received loading dose of 600 mg, including 86 *2 Carriers (13 homozygotes and 73 heterozygotes) and 260 *2 Non Carriers. Clopidogrel response, assessed with Platelet Reactivity Index VASP (PRI VASP), was significantly affected by genotypes with lower Clopidogrel Response in CYP2C19*2 allele carriers (p=0.01). Accordingly, the rate of clopidogrel non responders was higher in CYP2C19*2 allele carriers: 53% vs. 41%, p=0.04. All Clopidogrel non Responders (n=151), including 105 *2 Non Carriers and 46 *2 Carriers, received High 150 mg clopidogrel maintenance at discharge to overcome initial non response. After one month, High Maintenance dose overcame clopidogrel non response in only 44 % of the whole population and significantly less frequently in *2 Carriers than in Non Carriers, 28% vs. 50%, p=0.01.

Conclusion: Higher Clopidogrel Maintenance dose was able to overcome Clopidogrel Non Response in less than half of Clopidogrel Non Responders undergoing PCI for NSTE ACS. The benefit of this tailored Therapy was significantly reduced in CYP2C19*2 Carriers. Therefore, these patients might require alternative strategies with new P2Y12 blockers.

040

Fragmented QRS complex on a 12-lead ECG in patients with acute myocardial infarction: a MRI study.

Marion Angue [Orateur] (1), Luc Lorgis (1), Alexandre Cochet (2), Carole Richard (1), Alain Lalande (2), Marianne Zeller (3), Philippe Buffet (1), Isabelle L'Huillier (1), Francois Brunotte (2), Yves Cottin (1)
(1) CHU Bocage, Cardiologie, Dijon, France – (2) CHU Hôpital d'Enfants, Unité IRM et LE21, Dijon, France – (3) IFR 100 santé-STIC, LPPCE, Dijon, France

Objective: To investigate the relationship between fragmented QRS complex (fQRS) and parameters of infarct size (IS) and no reflow assessed by cardiac magnetic resonance (CMR) in patients with acute myocardial infarction.

Patients and methods: Patients with a fQRS were compared with patients without fQRS. CMR was performed in 246 consecutive patients within the week following the AMI. Early and late gadolinium-enhanced images were examined to assess IS and microvascular obstruction. Left ventricular ejection fraction (LVEF) and left ventricular volumes were also determined.

Results: 128 (52%) presented a fQRS on the first 12-lead ECG 36 hours post-AMI. Despite similar demographic, ECG and clinical features, patients with a fQRS were more likely to be male and had a higher systolic blood pressure on admission. Furthermore, patients with a fQRS had a significantly lower LVEF, and larger IS than did patients without fQRS as assessed by CMR. Interestingly, myocardial perfusion abnormalities after infarction determined by first-pass perfusion images (microvascular obstruction=MO) and late perfusion images (persistent MO=PMO) were significantly more frequent in the fQRS group (Table 1). By multivariate logistic regression analysis, only infarct size (OR=0.456; 95%CI: 1.03-1.07, p=0.001) was an independent predictor of a fragmented QRS.

▶